DIELS-ALDER REACTION OF THE DIHYDROPYRIDINONES V: APPROACH TO THE IRCINAL B CORE†

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Abstract-Thermal and high-pressure Diels-Alder reaction of the suitably assembled dihydropyridinones afforded the hydroisoquinoline derivatives, which were transformed to the key intermediates for the ABC substructure of ircinal B.

During the course of our investigation on the total synthesis of the marine alkaloid manzamine A (**1**), an efficient intermolecular Diels-Alder (D-A) reaction of some dihydropyridinone derivatives with a siloxydiene has been devised for the construction of the AB hydroisoquinoline ring system,[1] which is the common framework of this marine alkaloid family (manzamines A, B, D etc.). Related synthetic approaches so far reported are directed to this manzamine A type substructures[2] and no obvious synthetic study has been announced concerning the manzamine B type structure. Considering the biogenetic theory proposed by Baldwin,[3] implying the prior formation of manzamine B (**2**), which is then transformed to the more complex manzamine A (**1**), we now focused on the synthetic approach to the ABC ring system of ircinal B (**3**), which contains a characteristic 11-membered azacyclic ring.

As an extension of our D-A strategies,[1] we envisaged the retrosynthetic route for the ABC substructure of ircinal B employing the selected dihydropyridinones (**6**, **7**) as starting dienophiles (**Scheme 1**).

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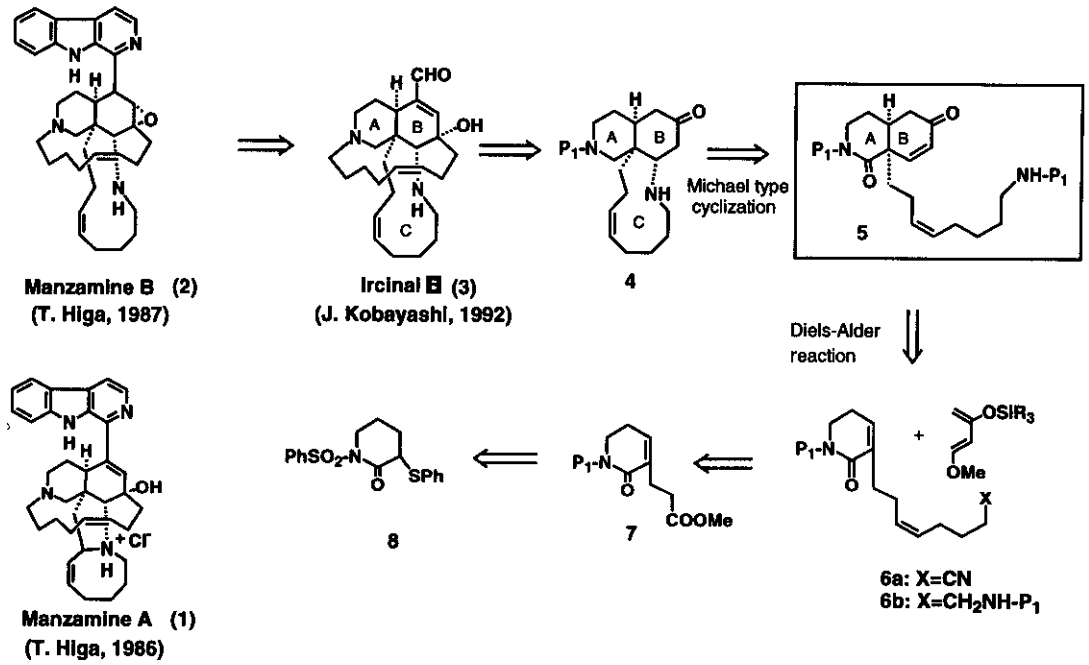
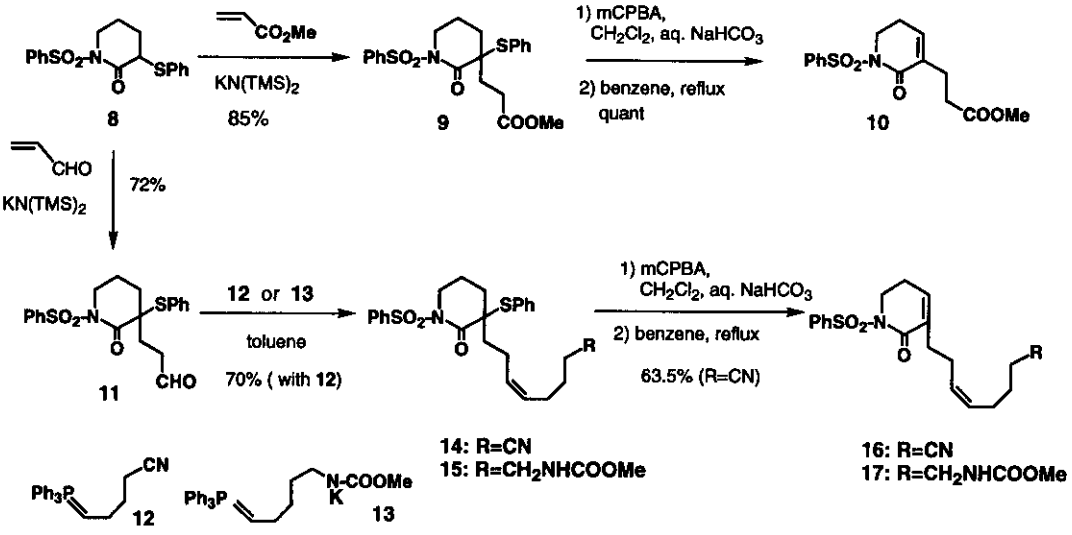
†This paper is dedicated to the memory of the late Professor Yoshio Ban.

Scheme 1: Retrosythetic analysis for manzamine B and ircinal B



Scheme 2: Preparation of the dienophiles



Obviously these dienophiles are simpler than those used in our manzamine A studies[1] and it is our aim to find a more convenient way to reach a complex manzamine A (ircinal A) core by conversion from manzamine B. Detailed herein is our D-A approach to a key intermediate for ircinal B type basic skeleton and related transformations along these lines.

Results and Discussion

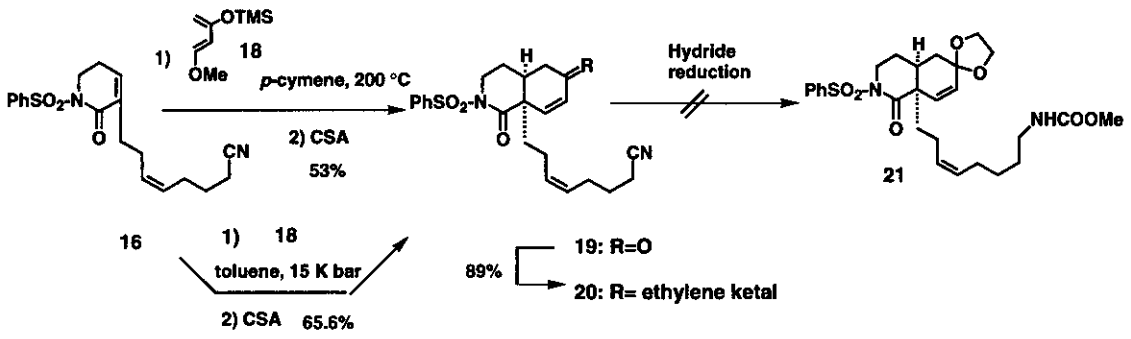
Preparation of the Dienophiles

According to the retrosynthetic scheme shown (**Scheme 1**), we started to prepare the dienophiles (**6**, **7**) from *N*-benzenesulfonyl-3-phenylthio-2-piperidone (**8**). As we have reported,[1] all these dihydropyridinones were easily prepared *via* the Michael reaction with methyl acrylate or acrolein.[4] The new dihydropyridinones (**16**, **17**) bearing long chains with proper nitrogen functionality were obtained *via* the Wittig reaction of the aldehyde (**11**) with the ylide (**12**) generated from (4-cyanobutyl)triphenylphosphonium bromide, or the reaction with the carbamate ylide (**13**) from (5-carbomethoxyaminopentyl)triphenylphosphonium bromide as shown in **Scheme 2**. It should be noted that the Wittig reaction with **12** proceeded without difficulty, while the Wittig reaction with **13** was not successful for a large scale operation. Usefulness of the ylide (**12**) stemmed not only from the effective Wittig reaction but also from the easiness of its preparation. The most probable reason for the messy reaction with **13** was due to the susceptibility of *N*-arylsulfonyllactam towards a nucleophile, as has already been encountered in our previous research.[1]

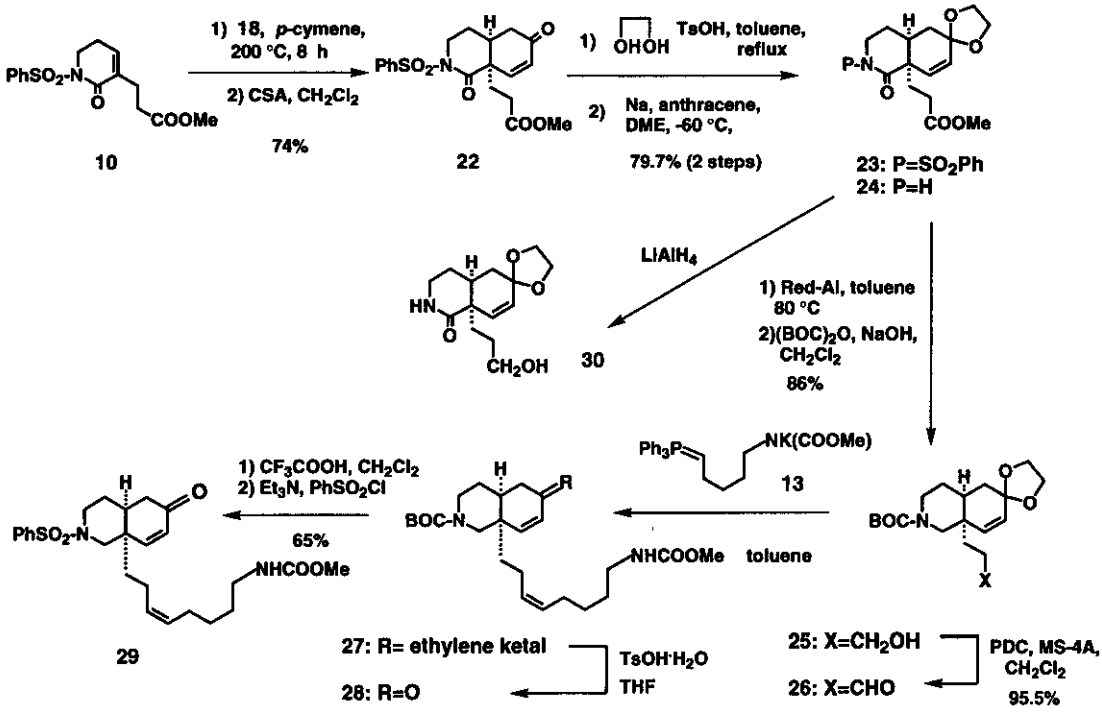
Diels-Alder Reaction and Subsequent Transformation

With the requisite dienophiles in hand, we next surveyed their D-A reaction under high pressure conditions as well as normal (thermal) conditions. Thus, a thermal D-A reaction of **16** with the Danishefsky's diene (**18**) was carried out to give the desired adduct (**19**) in a satisfactory yield (53%), while an attempted reaction with *NH*-containing dienophile (**17**) met with total failure. In order to improve the yield, a high pressure D-A reaction of **16** was pursued. The D-A reaction of **16** with **18** proceeded smoothly in toluene at room temperature under high-pressure conditions (15 Kb, 4 days) to afford the enone (**19**) in 65.6% after acid treatment. Although a remarkable increase in the yield of **19** was not observed, a cleaner reaction was observed when compared with the thermal one, thus made the work-up steps easier. Towards an intermediate (**21**), the adduct (**19**) was first transformed to the ketal (**20**). Attempted hydride reduction of the CN-functionality in **20** to the NH_2-group was more than a straightforward transformation. Neither the typical reduction conditions

Scheme 3: Diels-Alder reaction with the CN-containing dienophiles



Scheme 4: Practical route for the key intermediates



($LiAlH_4$-THF) nor the milder conditions ($NaBH_4$-$ZrCl_4$ etc.) gave an unequivocal reduction product, only resulting in messy mixtures. Through these abortive steps, we decided to obtain a base-stable intermediate such as **25**, in which the labile lactam carbonyl was reduced to a methylene unit. Thus, we employed the simple dihydropyridinone (**10**) as the most practical dienophile partner. Thermal D-A reaction proceeded without event to afford the enone (**22**) in 74% yield from **10**. Protection with ketal and *N*-deprotection by sodium anthracenide gave the *NH*-lactam (**24**) in 79.7% (2 steps). Crucial lactam reduction was achieved by excess Red-Al at 80 °C, followed by the *N*-protection with BOC group to furnish the alcohol (**25**) in 86%. On the other hand, $LiAlH_4$ reduction of **24** afforded the partial reduction product (**30**).

In an attempt to obtain a corresponding *N*-benzenesulfonyl derivative, an unexpected cyclized compound (**31**) was formed exclusively (72%) by the treatment with $PhSO_2Cl$ after Red-Al reduction, while normal *N*-methoxycarbonyl derivative (**32**) was obtained (55%) in a similar reaction sequence using ClCOOMe (**Scheme 5**). The structure of the cyclized product (**31**) obtained was fully characterized not only by spectroscopic means but also by X-ray crystallography as shown in **Figure 1**.

Oxidation of **25** by PDC gave the aldehyde (**26**), which was treated with the above-mentioned Wittig ylide (**13**) to afford the olefin (**27**) along with the inseparable by-product. Deketalization of **27** afforded the *N*-BOC enone (**28**) without event. For the elaboration of the 11-membered azacyclic ring through a Michael-type cyclization, it is desirable to use an acid-stable *N*-protecting group such as arylsulfonyl group. In this regard, we prepared the *N*-benzenesulfonyl derivative (**29**) through the sequence shown in **Scheme 4**.

Scheme 5: Red-Al reduction and *N*-protection sequence

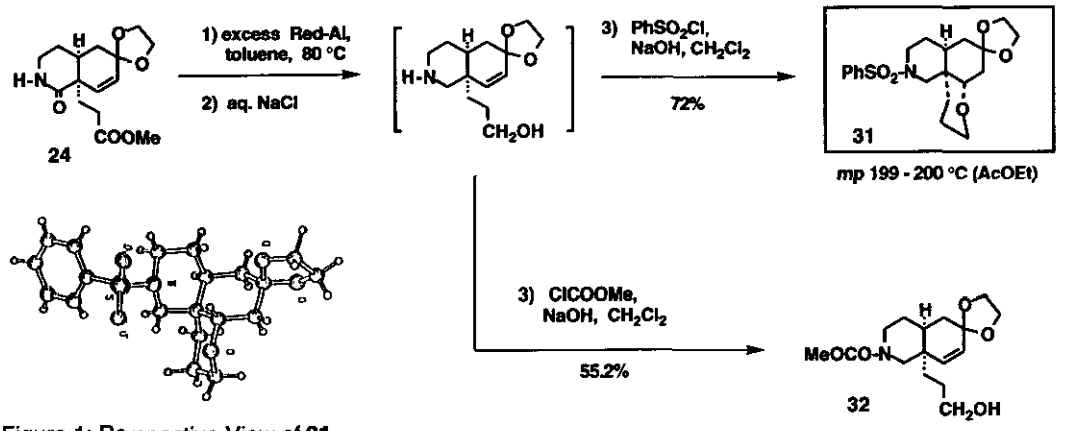


Figure 1: Perspective View of **31**

The enones (**28, 29**) obtained here might be a useful precursor for the construction of the ABC azacyclic skeleton of ircinal B (**3**), and studies along these lines are in progress and will be reported in due course.

EXPERIMENTAL

General: Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra (υ in cm^{-1}) were recorded with a Hitachi 260-10 spectrophotometer. Unless otherwise noted, ir spectra refer to KBr disks. Ms were recorded on a Hitachi M-60, RMU-7, JEOL HX-110, or JMS-AM 20 mass spectrometer. Proton and carbon nuclear magnetic resonance (^1H- and ^{13}C-nmr) spectra were recorded on JEOL GSX-400, JNM-GSX-500, JNM-GSX-400A, and JNM-GSX-500A apparatus. Nmr spectra were measured in $CDCl_3$, unless otherwise noted, and chemical shifts were recorded in δ values (ppm) relative to Me_4Si internal standard. Microanalyses were performed on a Perkin Elmer 240 C, H, N analyzer. All reactions were carried out under argon atmosphere and column chromatography is performed with Merck SiO_2 60 unless otherwise specified. Preparation of **9** and **11** has already been reported in the previous paper.[4]

Wittig Olefination Reaction of 11 with 12

A) A mixture of bromovaleronitrile (16.0 g, 98.7 mmol) and triphenylphosphine (20.0 g, 76.3 mmol) in toluene (50.0 ml) was stirred under reflux for 4 h. The precipitated material was filtered after cooling, and dried under vacuum (80 °C, 2 h) to afford the phosphonium bromide (22.3 g, 68.9%) as a white powder: mp 226 °C; ir 2890, 2800, 2250, 1590, 1485 cm^{-1}.

B) To a stirred suspension of the phosphonium bromide prepared above (5.28 g, 12.4 mmol, dried prior to use) in dry toluene (80 ml) was added $KN(TMS)_2$ (2.13 g, 10.7 mmol, Fluka) at room temperature. The resulting red ylide solution was kept stirring for 0.5 h. To this was added the aldehyde (**11**) (2.00 g, 4.96 mmol) as solid and the mixture was kept stirring for 1.5 h at room temperature. The mixture was quenched by the addition of sat. aq. NH_4Cl (30 ml) and extracted with AcOEt (100 ml x 3). Combined organic layer was washed with brine (20 ml x 2) and dried over $MgSO_4$. Concentration of the solvent gave a crude residue, which was purified by column chromatography (100 g, AcOEt / *n*-hexane=1 / 3) to afford the desired olefin (**14**) (1.63 g, 70%) as a white solid: mp 89-90 °C (AcOEt / *n*-hexane); ir 2900, 2260, 1680, 1480 cm^{-1}; ^1H-nmr δ (400 MHz) 1.15-1.17 (4H, m), 2.05-2.17 (8H, m), 2.22 (2H, t, *J*=7.2 Hz), 2.22-2.27 (1H, ddd, *J*=5.9, 9.8, 16.8 Hz), 5.22-5.25 (1H, m), 5.22-5.23 (1H, m), 5.26-5.30 (1H, m), 6.96-6.98 (2H, m), 7.12-7.16 (2H, m), 7.30-7.33 (1H, m), 7.55-7.58 (2H, m), 7.66-7.69 (1H, m), 8.05-8.07 (2H, m); HRFABms Calcd for $C_{25}H_{29}N_2O_3S_2$ (MH^+): 469.1623; Found: 469.1623.

***N*-Benzenesulfonyl-3-(7-cyano-3-heptenyl)-5,6-dihydro-2*(1H)*-pyridinone (16)**

To a cooled (-8 °C) and stirred solution of the Wittig product (**14**) (468 mg, 1.0 mmol) and Cs_2CO_3 (65.2 mg, 0.2 mmol) in CH_2Cl_2 (20 ml) was added slowly a CH_2Cl_2 (10 ml) solution of mCPBA (216 mg, 80%, 1.0 mmol) by a pipette. After being

stirred at this temperature for 1.5 h, the mixture was diluted with brine (30 ml) and extracted with AcOEt (100 ml). The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a crude product, which was taken into benzene (20 ml) and heated under reflux for 1 h. After evaporation of the solvent, the residue was purified by column chromatography (40 g, AcOEt / *n*-hexane=3 / 10) to afford the desired dihydropyridinone (**16**) (341 mg, 63.5%) as a pale yellow oil; ir (neat) 2940, 2250, 1690, 1450 cm^{-1}; ^1H-nmr δ (400 MHz) 1.60 (7H, m), 2.29 (5H, m), 4.05 (2H, t, *J*=6.6 Hz), 5.27 (1H, m), 5.36 (1H, m), 6.55 (1H, t, *J*= 4.5 Hz), 7.55 (2H, m), 7.63 (1H, m), 8.03 (2H, m); LREIms m/z: 358 (M^+, 5).

High Pressure Diels-Alder Reaction of 16 with Danishefsky's Diene

A solution of the dienophile (**16**) (830 mg, 2.32 mmol) and diene (**18**) (2.00 ml, 10.3 mmol) in dry toluene (2.5 ml) was sealed in a Teflon tube and kept at 15 Kb for 4 days at room temperature. After being removed from the apparatus, the mixture was diluted with AcOEt and concentrated to give an yellow oil, which was taken into CH_2Cl_2 (10 ml) and stirred at room temperature for 0.5 h in the presence of CSA (60 mg, 0.25 mmol). After being quenched by the addition of sat. aq. $NaHCO_3$ (7 ml) and AcOEt (15 ml), the mixture was extracted with AcOEt (100 ml) and worked up as usual. The crude material (1.5 g) thus obtained was purified by column chromatography (50.0 g, Et_2O / *n*-hexane=20 /1) to afford the pure enone (**19**) (647.6 mg, 65.6%) as an yellow oil, which was crystallized from AcOEt-*n*-hexane affording a white crystal: mp 112-113 °C; ir 2960, 2940, 2250, 1680, 1450 cm^{-1}; ^1H-nmr δ (500 MHz) 1.65-1.71 (5H, m), 1.97-2.02 (1H, m), 2.05-2.07 (2H, m), 2.08-2.12 (3H, m), 2.35 (2H, t, *J*= 7.2 Hz), 2.37 (1H, m), 2.60-2.62 (1H, m), 2.70 (1H, ddd, *J*=5.2, 5.4, 16.8 Hz), 3.79-3.8 (1H, m), 4.06-4.12 (1H, m), 5.26-5.35 (2H, m), 5.95 (1H, d, *J*=10.1 Hz), 6.65 (1H, d, *J*=8.9 Hz), 7.55 (2H, t, *J*=7.5 Hz), 8.03 (2H, m); LREIms m/z: 426 (M^+, 5), 305 (100).

Thermal Diels-Alder Reaction of 16 with Danishefsky's Diene

A mixture of the dienophile (**16**) (1.10 g, 3.07 mmol) and diene (**18**) (5.0 ml, 25.7 mmol) in dry *p*-cymene (13.0 ml) was heated under reflux (bath temp. ~200 °C) for 20 h. After removing the solvent under reduced pressure, the residue (~1.50 g) was taken into CH_2Cl_2 (30 ml) and stirred at room temperature for 0.5 h in the presence of CSA (60 mg, 0.25 mmol). The dark mixture was quenched by the addition of sat. aq. $NaHCO_3$ (20.0 ml) and ether (50 ml), and the mixture was extracted with AcOEt (100 ml x 2) and worked up as usual. The crude material thus obtained was purified by column chromatography (150.0 g, Et_2O / *n*-hexane=20 / 1) to afford the pure enone (**19**) (700.0 mg, 53.0%).

Ketalization of the Enone (19)

A solution of the enone (**19**) (127.8 mg, 0.3 mmol), ethylene glycol (0.25 ml, 4.50 mmol) and PPTS (15.1 mg, 0.06 mmol) in toluene (5 ml) was heated under reflux for 7 h. The mixture was diluted with AcOEt (15 ml) and sat. aq. $NaHCO_3$ (5.0 ml) and stirred for 5 min. The mixture was extracted with AcOEt and washed with brine. Evaporation of the dried ($MgSO_4$) solvent gave a crude material, which was purified by column chromatography (15.0 g, Et_2O / *n*-hexane = 5 / 1) to afford the ketal (**20**)

(125.3 mg, 89%) as an yellow oil, which was recrystallized from AcOEt / *n*-hexane to furnish a white crystal: mp 101-102 °C; ir 2950, 2240, 1160, 1470, 1450 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.70-1.72 (3H, m), 1.77-1.83 (3H, m), 1.93-1.96 (3H, m), 2.08-2.11 (5H, m), 2.31-2.355 (3H, t-like), 3.90-3.97 (6H, m), 5.60 (1H, d, *J*=10.1 Hz), 5.76 (1H, d, *J*= 10.1 Hz), 7.52 (2H, t, *J*= 7.6 Hz), 7.62 (1H, t, *J*= 7.6 Hz), 8.01 (2H, d-like); LREIms m/z: 470 (M^+, 5).

_N_-Benzenesulfonyl-3-(2-methoxycarbonyl)-5,6-dihydro-2(*1H*)-pyridinone (10)

To a cooled (-10.0 °C) and stirred solution of the ester (**9**) (21.25 g, 57.58 mmol) in CH_2Cl_2 (500 ml) and sat. aq. $NaHCO_3$ (75 ml) was added dropwise a solution of mCPBA (12.89 g, 31.32 mmol) in CH_2Cl_2 (100 ml). After stirring for 1 h, the mixture was diluted with brine and sat. aq. $NaHCO_3$ and organic layer was separated. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with brine, dried with $MgSO_4$ and concentrated to afford the residue. The crude product was purified by column chromatography (100 g, Et_2O / *n*-hexane =5 / 1) to give the pure dienophile (**10**) (21.02 g, quant): mp 76.0-80.0 °C (Et_2O / *n*-hexane); ir 2960, 1730, 1680, 1550 cm^{-1}; ^{1}H-nmr δ (500 MHz) 2.39-2.55 (2H, q, *J*=7.6 Hz), 2.59-2.55 (4H, m), 3.61 (3H, s), 5.05 (2H, t, *J*=6.6 Hz), 6.62 (1H, t, *J*=5.3 Hz), 7.55 (2H, t, *J*=7.5 Hz), 7.63 (1H, t, *J*=7.3 Hz), 8.03 (2H, d, *J*=7.3 Hz); LREIms m/z: 323 (M^+, 10). *Anal.* Calcd for $C_{15}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 5.33. Found: C, 55.68; H, 5.21; N, 5.33.

Thermal Diels-Alder Reaction of 10 with Danishefsky's Diene

To a preheated (70 °C) solution of the diene (**18**) (10.7 ml, 55.0 mmol) in *p*-cymene (35 ml, distilled and degassed) was added the dienophile (**10**) (3.55 g, 11.0 mmol, as powder) and the whole was heated at 200-220 °C for 8 h. After being stirred at room temperature for overnight, the mixture was carefully concentrated by evaporator (at ~80 °C) to give an orange residue, which was further concentrated under vacuum. The crude product (as silyl enol ether) was then taken into CH_2Cl_2 (60 ml) and treated with CSA (178 mg, 0.55 mmol) at room temperature for 1 h. After being quenched by the addition of sat. aq. $NaHCO_3$ and extracted with AcOEt (~200 ml), the organic layer was worked up as usual to give the crude product (7.50 g), which was filtered through a silica gel short column (100 g, CH_2Cl_2) to remove the less polar material. Further elution with CH_2Cl_2-MeOH (20 / 1) as eluent gave nearly pure product, which was recrystallized from ether-AcOEt to afford the crystalline product (**22**) (1.60 g). After concentration of the mother liquor, further amount of the product (1.57 g, total 3.19 g, 74%) was obtained through a chromatographic purification (50.0 g, AcOEt / *n*-hexane =1 / 1). **22**: white crystals, mp 166.5-167.5 °C (AcOEt); ir 2950, 1470, 1700, 1680, 1350 cm-1; ^{1}H-nmr δ (500 MHz) 1.88-1.95 (1H, m), 1.99-2.03 (1H, m), 2.13-2.18 (2H, m), 2.25-2.30 (2H, m), 2.35 (1H, dd, *J*=5.2, 12.6 Hz), 2.41-2.45 (1H, m), 2.73 (1H, m), 2.77-3.85 (1H, m), 3.63 (3H, s), 4.06-4.12 (1H, m), 5.99 (1H, d, *J*=10.3 Hz), 6.63 (1H, d, *J*=10.3 Hz), 7.55 (2H, t, *J*=7.5 Hz), 7.66 (1H, t, *J*=7.5 Hz), 8.02 (2H, d, *J*=7.5 Hz); LREIms m/z: 391 (M^+, 10), 360 (5). *Anal.* Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58. Found: C, 58.49; H, 5.18; N, 3.53.

Transformation to the Ketal Lactam (24)

A solution of the enone (**22**) (6.04 g, 15.43 mmol), ethylene glycol (12.94 ml, 23.0 mmol) and PPTS (0.86 g, 5.11 mmol) in toluene (400 ml) was heated under reflux for 5 h. After being quenched with sat. aq. $NaHCO_3$, the mixture was extracted with AcOEt and worked up as usual to give almost pure ketal (**23**) (7.54 g): colorless amorphous; ir 2950, 2890, 1730, 1680 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.76 (1H, m), 1.90-2.00 (3H, m), 2.02-2.21 (5H, m), 3.62 (3H, s), 3.91-3.96 (6H, m), 5.65 (1H, d, *J*=10.1 Hz), 5.73 (1H, d, *J*=10.1 Hz), 7.52 (2H, t, *J*=7.9 Hz), 7.62 (1H, t, *J*=7.7 Hz), 7.99 (2H, d, *J*=7.3 Hz).

The unpurified material was directly subjected to desulfonylation as follows. To a cooled (-60 °C) and stirred solution of the ketal (**23**) (7.50 g, ~17.31 mmol) was added a blue-black solution of sodium anthracenide [60.2 ml; prepared from Na (2.25 g, 98.7 mmol), anthracene (20.0 g, 112.3 mmol) in DME (150 ml) as described by Johnson[5]]. After being stirred for 0.5 h, the yellow mixture was quenched by the addition of sat. aq. NH_4Cl (20 ml) followed by the dilution with CH_2Cl_2 (300 ml). The organic layer was separated and aqueous layer was re-extracted with CH_2Cl_2 (200 ml). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give a crude solid mass, which was purified by column chromatography (300 g, CH_2Cl_2 → AcOEt / MeOH = 10 / 1) to afford the *NH*-lactam (**24**) (3.63 g, 79.7%) as a white solid: mp 197-199 °C; ir 3240, 2940, 2880, 2320, 1740, 1730, 1660, 1605 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.76-2.00 (3H, m), 2.02-2.25 (4H, m), 2.25-2.40 (2H, m), 3.20-3.40 (2H, m), 3.65 (3H, s), 3.85-4.00 (4H, m), 5.70 (1H, d, *J*=10.1 Hz), 5.96 (1H, d, *J*=10.1 Hz), 6.13 (1H, br s); LREIms m/z: 295 (M^+, 10). *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 66.97; H, 7.19; N, 4.70.

Reduction of 24 to the Alcohol (25)

To a stirred solution of the *NH*-lactam (**24**) (1.0 g, 3.39 mol) in toluene (30.0 ml) was added a toluene solution of Red-Al (~9.0 ml, ~30 mmol). The resulting mixture was heated at 80 °C (bath temp.) for 1 h. After being quenched by the slow addition of brine (5 ml), the mixture was diluted with THF (80 ml) and aq. NaOH solution (prepared from NaOH 406 mg + H_2O 5 ml) with vigorous stirring. To this mixture was then added $(BOC)_2O$ (1.10 g, 5.0 mmol) and kept stirring for 2 h. Stirrig was continued for 1 h more after addition of CH_2Cl_2 (50 ml) to dissolve the intermediate. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (300 ml). The organic layer was washed with brine (10 ml) and dried over $MgSO_4$. Concentration of the solvent gave a crude product (2.32 g), which was purified by column chromatography (100 g, CH_2Cl_2), affording the alcohol (**25**) (1.03 g, 86%) as a colorless oil; ir (neat) 3450, 2925, 2850, 1680, 1660, 1420 cm^{-1}; ^{1}H-nmr δ (500 MHz): 1.30-1.70 (9H, m), 1.75-2.00 (4H, m), 2.00-2.15 (2H, m), 2.85-3.00 (2H, m), 3.45-3.65 (4H, m), 3.89-4.03 (3H, m), 3.70- 4.00 (5H, m), 5.55-5.65 (2H, m); LRFABms m/z: 354 (MH^+, 41), 298 (100); HRFABms Calcd for $C_{19}H_{32}NO_5$ (MH^+): 354.2280; Found: 354.2280.

Oxidation to the Aldehyde (26)

PDC (1.0 g, 2.66 mmol) and powdered MS-4A (0.5 g, activated) were placed in a flask and the whole was dried well under vacuum for 1 h under Ar. To a stirred suspension of the PDC-MS-4A in dry CH_2Cl_2 (10.0 ml) was added a CH_2Cl_2 (5 ml) solution of

the *N*-BOC alcohol (**25**) (353 mg, 1.0 mmol) and the whole was kept stirring for 3 h, followed by sonication for 0.5 h. The mixture was then diluted with ether (~50 ml) and proper portion of $MgSO_4$ was delivered to make filtration easier. Filtration and washing of the solid mass with ether gave a residue after evaporation (caution: do not evaporate the solvent completely). The residue was directly purified by column chromatography (AcOEt / *n*-hexane= 1 / 2) to afford the desired aldehyde (**26**) (265 mg, 95.5%) as a colorless oil; ir (neat) 2975, 2925, 2850, 1720, 1680, 1480, 1420 cm-1;^{1}H-nmr δ (500 MHz) 1.33 (1H, d-like), 1.46 (9H, br s), 1.60-1.80 (3H, m), 1.85-2.20 (4H, m), 2.42 (2H, br s), 2.80-3.00 (2H, m), 3.50-3.80 (1H, m), 3.85- 4.05 (4H, m), 5.45-5.60 (1H, m), 5.69 (1H, d-like), 9.77 (1H, br s); LRFABms m/z: 352 (MH^+, 60); HRFABms Calcd for $C_{19}H_{30}NO_5$ (MH^+): 352.2125; Found: 352.2126.

Wittig Reaction of 26 with the Ylide (13)

A) Preparation of the Wittig salt (5-methoxycarbonylaminopentyltriphenylphosphonium bromide) was conducted as follows. To a cooled (0 °C) and stirred suspension of 5-amino-1-pentanol (15.0 g, 145 mmol) and K_2CO_3 (15.0 g, 108.7 mmol) in CH_2Cl_2 (150 ml) was added ClCOOMe (12.3 ml, 130.0 mmol). The mixture was kept stirring at room temperature for 1 h and quenched by the dilution with brine (30 ml) and AcOEt (200 ml). Extraction with AcOEt and usual work-up gave a crude product (17.8 g), which was purified by silica gel short column (AcOEt / *n*-hexane =1 / 1) to furnish pure 5-methoxycarbonylamino-1-pentanol (17.3 g, 73.8%) as a colorless oil. To a cooled (5 °C) and stirred solution of the carbamate alcohol prepared above (4.5 g, 27.9 mmol) and triphenylphosphine (8.05 g, 30.7 mmol) in dry CH_2Cl_2 (50 ml) was added crystalline carbon tetrabromide (10.1 g, 30.7 mmol) in one portion. An exothermic reaction was observed and stirring was continued for 1 h under these conditions. Being concentrated to a half of original volume, the mixture was diluted with cold ether (~200 ml) and kept in an ice-bath for 0.5 h. After filtration of the precipitated material (phosphine oxide), the filtrate was concentrated to give a crude product, which was purified by column chromatography (100g, AcOEt / *n*-hexane =1 / 2) to afford the pure 5-bromo-1-methoxycarbonylaminopentane (5.55 g, 88.6%) as a white solid mass: mp 44-46 °C (ether / *n*-hexane); ir 3400, 1720 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.44-1.65 (4H, m), 1.85-1.91 (2H, m), 3.19 (2H, t like), 3.41 (2H, t, *J*=6.7 Hz), 3.66 (3H, br s), 4.70 (1H, br); LRFABms m/z: 224 (MH^+, 100), 226 (MH^+, 92). *Anal.* Calcd for $C_7H_{14}NO_2Br$: C, 37.52; H, 6.30; N, 6.25, Found: C, 37.51; H, 6.18; N, 6.22.

A solution of 5-bromo-1-methoxycarbonylaminopentane (13.44 g, 60 mmol) and triphenylphosphine (28 g, 66 mmol) in dry toluene (80 ml) was heated under reflux for 48 h. After being kept in an ice bath for 0.5 h, the precipitated material was filtered and washed with cold ether (~200 ml). Thus obtained phosphonium salt was dried at 50 °C for 4 h under vacuum to afford the pure Wittig salt as a white solid: mp 167-168 °C (AcOEt); ir 3470, 3375, 3220, 3020, 2900, 1670, 1520, 1430 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.60-1.75 (6H, m), 3.13 (2H, q like), 3.59 (3H, br s), 3.76 (2H, m), 5.92 (1H, br s), 7.68-7.85 (15H, m).

B) The phosphonium bromide prepared above (3.99 g, 8.2 mmol) was dried at 80 °C for 3 h under vacuum in a reaction flask and suspended in toluene (30 ml). To this was added $KN(TMS)_2$ (4.10 g, 20.5 mmol) at room temperature and resulting red ylide

solution was kept for 0.5 h. A solution of the aldehyde (**26**) (800 mg, 2.28 mmol) in toluene (5 ml) was added and stirring was continued for 1 h. The mixture was then diluted with ether and sat. aq. NH_4Cl and extracted with AcOEt. AcOEt layer was washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a residue, which was purified by column chromatography (AcOEt / *n*-hexane =1 / 2) to afford the olefin (**27**) (850 mg, 78%, contaminated with the by-product). Further purification with the column chromatography (AcOEt / *n*-hexane =1 / 2) afforded the nearly pure material as a colorless oil; ir (neat) 3350, 2950, 2850, 1725, 1700, 1540, 1440 cm-1; ^{1}H-nmr δ (500 MHz) : 1.25-1.55 (12H, m), 1.60-1.80 (3H, m), 1.80-2.20 (10H, m), 2.80-3.20 (4H, m) 3.50 (1H, d-like), 3.66 (3H, br s), 3.85-4.10 (4H, m), 4.75-4.90 (1H, br), 5.30-5.35 (2H, m), 5.55-5.70 (2H, m); LRFABms m/z: 479 (MH^+, 30), 379 (100); HRFABms Calcd for $C_{26}H_{43}N_2O_6$ (MH^+): 479.3121; Found: 479.3121.

Ketal Deprotection of 27 to the *N*-BOC Enone (28)

To a stirred solution of the olefin (**27**) (90 mg, 0.18 mmol) in THF (8 ml) was added $TsOH{\cdot}H_2O$ (45 mg, 0.23 mmol) in one portion at room temperature. Resulting mixture was kept stirring at room temperature until no further change was observed on tlc. Then the mixture was quenched by the addition of sat. aq. $NaHCO_3$ and extracted with AcOEt (100 ml). The organic layer was washed well with sat. aq. $NaHCO_3$ (10 ml) and brine. After drying over $MgSO_4$, solvent was removed under reduced pressure to afford crude material, which was purified by column chromatography (20 g, AcOEt / *n*-hexane = 1/ 2) to give the nearly pure *N*-BOC enone (65 mg, 80.5%); ir (neat) 3925, 2925, 1720, 1700, 1690, 1685 cm-1; ^{1}H-nmr δ (500 MHz) : 1.25-1.40 (2H, m), 1.40-1.52 (1H, m), 1.60 (10H, br s), 2.04 (5H, m), 2.10-2.20 (1H, m), 3.10-3.20 (5H, m), 3.65 (7H, br s), 4,72 (2H, br s), 5.30-5.37 (3H, m), 6.02 (1H, d like), 6.65-6.85 (1H, br s); LREIms m/z: 377 (M-^{t}Bu, 30), 379 (100).

Conversion to the *N*-Benzenesulfonyl Enone (29)

To a stirred solution of the *N*-BOC enone (**28**) (35 mg, 0.08 mmol) in CH_2Cl_2 (5 ml) was added at room temperature an excess CF_3COOH (0.5 ml) and the resulting mixture was kept stirring for 2 h. Resulting yellow mixture was quenched by the addition of sat. aq. $NaHCO_3$ (total 5 ml) slowly. After foaming had subsided, K_2CO_3 was added and stirring was continued for 2 h. To this mixture was then added $PhSO_2Cl$ (1.5 ml) dropwise, and resulting mixture was kept stirring for 3 h. The mixture was diluted with AcOEt (~50 ml) and extracted with AcOEt. The organic layer was worked up as usual and concentrated to give a crude product (50 mg) as an yellow oil, which was further purified by column chromatography (AcOEt / *n*-hexane =1 / 1) to give the pure product (**29**) (20 mg, 55%) as a colorless oil; ir (neat) 3350, 1725, 1700, 1670 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.30-1.40 (2H, m), 1.45-1.60 (3H, m), 1.50-1.70 (4H, m), 1.95-2.20 (4H, m), 2.20-2.30 (1H, m), 2.50-2.80 (3H, m), 3.10-3.20 (2H, m), 3.20-3.40 (2H, m), 3.66 (3H, s), 4.75 (1H, br s), 5.30-5.45 (2H, m), 6.04 (1H, d-like), 6.77 (1H, d-like), 7.56 (2H, t-like), 7.62 (1H, m), 7.76 (2H, m); LRFABms m/z: 475 (MH^+, 90), 154 (100); HRFABms Calcd for $C_{25}H_{35}N_2O_5S$ (MH^+): 475.2267; Found: 475.2270.

Cyclic Ether (31)

To a stirred solution of the *NH*-lactam (**24**) (2.00 g, 7.78 mol) in toluene (60 ml) was added a toluene solution of Red-Al (30 ml, ~102 mmol). The resulting mixture was heated at 80 °C (bath temp.) for 1.5 h. After being quenched by the slow addition of brine (10 ml), the mixture was diluted with CH_2Cl_2 (150 ml) and aq. NaOH solution (from NaOH 1.35 g + H_2O 20 ml) with vigorous stirring. To this mixture was then added $PhSO_2Cl$ (4.0 ml, 22.6 mmol) and kept stirring for 2 h. Stirring was continued for 1 h more after addition of CH_2Cl_2 (50 ml) to dissolve the intermediate. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (300 ml). The organic layer was washed with brine (20 ml) and dried over $MgSO_4$. Concentration of the solvent gave a crude product (8.25 g), which was purified by column chromatography (400 g, CH_2Cl_2), affording the cyclic ether (**31**) (1.60 g, 86.1 %) as a colorless oil, which was further recrystallized from AcOEt to afford a colorless crystal: mp 199-200 °C; ir (neat) 3110, 2990, 2960, 1455, 1350, 1170, 1080 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.24-1.37 (2H, m), 1.46-1.59 (1H, m), 2.00-2.15 (1H, m), 1.62-1.67 (2H, m), 1.70-1.76 (2H, m), 1.90-1.94 (1H, m), 2.06-2.12 (1H, m), 2. 28 (1H, m), 2.52-2.58 (1H, m), 2.73 (1H, d-like), 2.93-2.95 (1H, d-like), 3.32-3.38 (1H, m), 3.43-3.51 (2H, m), 3.78-3.85 (2H, m), 3.90-3.95 (1H, m), 4.03-4.08 (2H, m), 7.51-7.55 (2H, m), 7.59-7.63 (1H, m), 7.71-7.74 (2H, m); LRFABms m/z: 394 (MH^+, 100), 307 (24); HRFABms Calcd for $C_{20}H_{28}NO_5S$ (MH^+): 394.1696; Found: 354.1696; *Anal.* Calcd for $C_{20}H_{27}NO_5S$: C, 61.05; H, 6.92; N, 3.56, Found: C, 61.12; H, 6.99; N, 3.58.

Crystal data for 31 ($C_{20}H_{27}NO_5S$; MW=393.50): a = 14.152 (2), b = 22.524 (2), c = 5.876 (2) Å, V = 1873.0 (7) Å ^{3}, Spacegroup: Orthorhombic, P2nb (Z = 4), Dx = 1.395g/cm^3, F(000) = 840, μ (Cu Kα) = 17.725 cm^{-1}. The diffraction experiment was carried out using a colorless transparent prismatic single crystal recrystalized from AcOEt solution with dimension of 0.2 x 0.2 x 0.1 mm. The four circle diffractometer AFC/5R (RIGAKU) was used with graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). 1656 Unique reflections (2θ<120°) were measured, of which 1359 with |Fo|>0 σ (Fo) were considered as observed. No absorption corrections were applied. The structure was solved by a direct method using SIR 85[6] and difference Fourier method. The refinement of atomic parameters was carried out using full matrix least-squares method with anisotropic temperature factors. All hydrogen atoms were located on the difference Fourier maps and refined with isotropic temperature factors. The atomic scattering factors were taken from "International Tables for X-ray crystallography"[7]. The final R value is 0.0474 (Rw=0.0492).

Reduction of 24 to the *N*-Methoxycarbonyl Alcohol (32)

To a stirred solution of the *NH*-lactam (**24**) (800 mg, 2.71 mol) in toluene (50 ml) was added a toluene solution of Red-Al (8.0 ml, 27.2 mmol). The resulting mixture was heated at 80 °C (bath temp.) for 1 h. After being quenched by the slow addition of brine (8 ml), the mixture was diluted with CH_2Cl_2 (80 ml) and 1N-NaOH solution (8 ml) with vigorous stirring. To this mixture was then added ClCOOMe (0.76 ml, 8.0 mmol) and kept stirring for 1 h. After completion of the reaction, the mixture

was extracted with AcOEt (300 ml). The organic layer was worked up as before to give a crude product (1.50 g), which was purified by column chromatography (106 g, CH_2Cl_2), affording the alcohol (**32**) (465.7 mg, 55.2 %) as a colorless oil; ir (neat) 3460, 2950, 1700, 1460 cm^{-1}; ^{1}H-nmr δ (500 MHz) 1.32-1.43 (1H, m), 1.45-1.60 (4H, m), 1.66-1.72 (3H, m), 1.91-1.98 (1H, m), 2.05-2.14 (2H, m), 2.88-3.08 (2H, m), 3.48-3.63 (3H, m), 3.68 (3H, s), 3.89-4.08 (4H, m), 5.50-5.65 (1H, br s), 5.66 (1H, d, J=10.0 Hz); LRFABms m/z: 312 (MH^+, 100); HRFABms Calcd for $C_{16}H_{26}NO_5$ (MH^+): 312.1811; Found: 312.1809.

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